UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte FERNANDO VALLE, NOEMI MEJIA, and ALAN BERRY

Appeal No. 2005-0394
Application No. 08/940,692

ON BRIEF

Before ADAMS, MILLS, and GREEN, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 23-27, 29-31, 33-40, 42-44 and 46-50. The examiner has indicated that the only other pending claims, claims 39, 40, 43, 47, 48 and 51 were allowable. See, Final Rejection, mailed March 26, 2003, page 11.

Claims 23, 27 and 38 are illustrative of the subject matter on appeal and are reproduced below:

23. A mutant host cell having a metabolic pathway which uses PEP as a precursor or inermediate of metabolism, said host cell characterized by:
    (a) being phenotypically Pts-/glu+ wherein the Pts- phenotype is caused by the deletion or inactivation of all or substantially all

of a gene selected from the group consisting of ptsI, ptsH and crr,
(b) requiring galactose permease activity to transport glucose; and
(c) having a specific growth rate on glucose as a sole carbon source of at least $0.4h^{-1}$.

27. A method for increasing PEP availability to a biosynthetic or metabolic pathway of a host cell, the method comprising,
a) obtaining a host cell mutant characterized by having a Pts-/glu+ phenotype requiring galactose permease activity to transport glucose; and having a specific growth rate on glucose as a sole carbon source of at least $0.4h^{-1}$ wherein the Pts- phenotype is caused by the deletion or inactivation of all or substantially all of one of the genes selected from the group consisting of ptsI, ptsH and crr; and
b) culturing the host cell mutant in the presence of an appropriate carbon source, wherein said host cell mutant utilizes PEP as a precursor or intermediate of metabolism.

38. A method for obtaining a Pts-/Glucose$^+$, glactose permease requiring-mutant cell, the method comprising:
(a) selecting a host cell which utilizes a phosphotransferase transport system;
(b) mutating the host cell whereby the phosphotransferase transport system is inactivated;
(c) culturing the mutant host cell under continuous culture conditions using glucose as a carbon source; and
(d) selecting mutant host cells which grow on glucose at a specific growth rate of at least $0.4h^{-1}$

The references relied upon by the examiner are:

Frost	5,168,056	Dec. 1, 1992
Ingrahm et al. (Ingrahm)	5,602,030	Feb. 11, 1997

Holms, "The Central Metabolic Pathways of Escherichia coli: Relationship Between Flux and Control Branch Point, Efficiency of Conversion to Biomass, and Excretion of Acetate," Curr. Topics Cell. Regulation, Vol. 28, pp. 66-105 (1986)

Saier et al. (Saier), "characterization of Constitutive Galactose Permease Mutants in Salmonella typhirmurium," J. Bacteriol, Vol. 113, No. 1, pp. 512-514 (1991)

GROUNDS OF REJECTION

Claims 23, 27, 38, 46 and 49 stand rejected under 35 U.S.C. § 103 as being unpatentable over Saier and Ingrahm.

Claims 23-27, 29-31, 33-38, 42, 44, 46, 49 and 50 stand rejected under 35 U.S.C. § 103 as being unpatentable over Frost, Holms, Ingrahm and Saier.

We reverse.

DISCUSSION

The Combination of Saier and Ingrahm:

According to the examiner (Answer, page 4) Saier

> teach methods of selecting a Pts^-/$glucose^+$ S. typhimurium strain comprising deleting the PTS genes (ptsH and ptsI), culturing the mutant cell using glucose as the sole available carbon source and selecting cells with a fast growth rate on glucose.[1] The mutant cells of Saier et al. use the galactose permease for the transport of glucose.... The fastest growth rate specifically obtained by the mutants of Saier et al. was 0.35/hr. Applicants claimed methods recite selecting cells with a growth rate of at least 0.4/hr.

In addition, the examiner finds (id.) Ingrahm

> Teach that it would be advantageous to increase the supply of PEP in a cell used for production of a desired product, in particular aromatic amino acid production, by modifying an enteric bacteria such as E. coli to use an alternative pathway from the PTS system for glucose uptake such that PEP production is not obligately coupled to glucose transport....

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[1] The examiner failed to identify, and we are unable to locate, exactly where Saier specifically teaches "selecting cells with a fast growth rate on glucose." Upon consideration of Saier, we find that the only selection criteria reported was that the cells "grew on glucose as the sole source of carbon." Saier, page 512, first column. While we recognize that Saier noted (id.) that the two strains selected for growth on glucose, happened to take up glucose "four to six times more rapidly than by the parental strains...", we find nothing in Saier, to suggest that the cells were selected for a fast growth rate on glucose.

Based on this evidence, the examiner concludes (Answer, page 5), "one of ordinary skill in the art would have been motivated to screen for Pts-/glucose+ cells such as those of Saier et al. with even higher growth rates than those specifically disclosed by Saier...." According to the examiner (id.), since Saier "disclose cells with growth rates very close to the claimed rate of at least 0.4/hr one of ordinary skill in the art would have reasonably expected to be able to obtain cells within the scope of the claims", specifically, cells having a specific growth rate on glucose as a sole carbon source of at least $0.4h^{-1}$.

What is unclear from the examiner's reasoning is where the prior art provides a suggestion to, screen cells for a fast growth rate on glucose, or more specifically to screen cells to obtain a growth rate of at least 0.4 h^{-1} as required by appellants' claimed invention. In this regard, we remind the examiner that prima facie obviousness based on a combination of references requires that the prior art provide "a reason, suggestion, or motivation to lead an inventor to combine those references." Pro-Mold and Tool Co. v. Great Lakes Plastics Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

> [E]vidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. . . . The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular.

In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (citations omitted). The suggestion to combine prior art references must come

from the cited references, not from the application's disclosure. See In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

As appellants point out (Brief, pages 9-13) there is nothing in the combination of references relied upon to suggest screening cells for the specific growth rate of 0.4 h^{-1}. Furthermore, we agree with appellants' argument (Brief, page 10),

> While one skilled in the art might hope to manipulate PTS^-/Glu^+ cells to have a higher growth rate there is no expectation, as taught in Saier, that one skilled in the art could reasonably expect to obtain a PTS^-/Glu^+ cell with a growth rate higher than 0.35 h^{-1} and at least 0.4 h^{-1} as presently claimed.

We are not persuaded by the examiner's speculation (Answer, page 10), that given the manner in which Saier reported the growth rate date, the actual growth rate reported in Saier could be anywhere between 0.28/hr up to 0.46/hr. In this regard, we remind the examiner that "[t]he Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because it may doubt that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis." In re Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968). Further, as discussed above, the examiner has failed to identify, and we cannot locate, a portion of the prior art relied upon that teaches screening cells for a fast growth rate on glucose, or more specifically to screen cells to obtain a growth rate of at least 0.4 h^{-1} as required by appellants' claimed invention.

Based on the foregoing, it is our opinion that the examiner failed to meet her burden[2] of establishing a prima facie case of obviousness. Accordingly, we reverse the rejection of claims 23, 27, 38, 46 and 49 under 35 U.S.C. § 103 as being unpatentable over Saier and Ingrahm.

The combination of Frost, Holms, Ingrahm and Saier:

According to the examiner (Answer, page 5), Frost teaches that by increasing the amount of substrate, and introducing one or more genes of the common aromatic pathway into a cell, you can increase both the carbon flow into the pathway, and the amount of final product obtained. In addition, the examiner finds (Answer, page 6), "Holms teaches that PEP within E. coli is consumed by several different metabolic pathways ... and the amount of PEP channeled into each of these pathways." The examiner relies on Ingrahm and Saier as set forth above.

Based on this evidence, the examiner finds (Answer, bridging paragraph, pages 7-8),

> [t]he disclosure of Saier et al. shows that it is possible to produce cells which are deleted in the PTS system yet still retain high growth rates on glucose.... [Thus] [i]t woud have been further obvious to one of ordinary skill in the art to select for such cells with high growth rates as such cells would be expected to be most useful for producing large amounts of aromatic amino acids. As Saier et al. disclose Pts^-/$glucose^+$ cells with growth rates very close to the claimed rate of at least 0.4/hr one of ordinary skill in the art would have reasonably expected to be able to obtain cells within the scope of the claims.

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[2] In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

What the examiner has not explained, is what in the combination of references relied upon, would motivate a person of ordinary skill in the art to screen for growth rates of at least 0.4/hr? The examiner admits (Answer, bridging sentence, pages 7-8) that Saier's cells "retain high growth rates on glucose." Therefore, why, in the absence of appellants' disclosure, would a person of ordinary skill in the art be motivated to screen for cells "having a specific growth rate on glucose as a sole carbon source of at least $0.4h^{-1}$"as set forth in appellants' claims.

As set forth in In re Kotzab, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000):

> A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. ... Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one "to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher."
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> ...
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> Most if not all inventions arise from a combination of old elements. ... Thus, every element of a claimed invention may often be found in the prior art. ... However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. ... Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. [citations omitted]

In other words, "there still must be evidence that 'a skilled artisan, ... with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.'" Ecolochem Inc. v.

Southern California Edison, 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1075-76 (Fed. Cir. 2000). On this record, the examiner has provided, and we find no evidence of a suggestion in the prior art to screen for cells having the specific growth rate set forth in appellants' claims. Accordingly, we reverse the rejection of claims 23-27, 29-31, 33-38, 42, 44, 46, 49 and 50 stand rejected under 35 U.S.C. § 103 as being unpatentable over Frost, Holms, Ingrahm and Saier.

REVERSED

Donald E. Adams)
Administrative Patent Judge)
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Demetra J. Mills) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
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Lora M. Green)
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